

# Thromboembolic complications in the group of hospitalized patients with atrial fibrillation – evaluation of the frequency and analysis of risk factors

Powikłania zakrzepowo-zatorowe u hospitalizowanych chorych z migotaniem przedsionków – ocena częstości występowania i analiza czynników ryzyka

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Lekarz Anna Stec jest absolwentką Wydziału Lekarskiego Uniwersytetu Medycznego w Lublinie. Obecnie odbywa szkolenie specjalizacyjne z kardiologii w I Klinice Kardiologii i Elektroterapii Świętokrzyskiego Centrum Kardiologii w Kielcach pod kierownictwem prof. dr hab. n. med. Beaty Wożakowskiej-Kapłon. Klinika ta specjalizuje się w diagnostyce i leczeniu zaburzeń rytmu serca (implantacja stymulatorów, ICD, CRT, badania elektrofizjologiczne, ablacje). Wolny czas dr Stec poświęca na jazdę na rowerze, grę w siatkówkę, pływanie.

## Abstract

**Introduction.** Thromboembolic complications are the most serious complications of atrial fibrillation (AF). Usually, they involve the central nervous system; however, embolism may also be located in the peripheral arteries. The aim of the study was to determine the frequency of thromboembolic complications and to identify the risk factors for their occurrence in hospitalized patients with AF.

**Materials and methods.** The study group consisted of 962 patients with non-valvular AF who were hospitalized in a reference cardiology center in 2007–2009. The risk of thromboembolic events in patients with AF were determined using CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scales.

**Results.** In the examined group of 962 patients with AF, the majority of patients (n = 674, 70%), were at the age of more than 70 years and 467 patients (48.5%) had permanent AF. No differences in frequency of arrhythmia between men and women were found. The majority of examined patients were at high risk of thromboembolic events as indicated by CHADS<sub>2</sub> score – 869 patients (90.3%) and CHA<sub>2</sub>DS<sub>2</sub>VASc score – 882 patients (91.7%). The mean CHADS<sub>2</sub> score was 2.4 points, while mean CHA<sub>2</sub>DS<sub>2</sub>VASc score – 4.2 points. The most common condition, and at the same time a thromboembolic risk factor included in the CHADS<sub>2</sub> scale, was hypertension found in 763 patients (79.3%). The majority of patients (n = 578, 60.1%) had also impaired renal function. Thromboembolic complications occurred in 162 patients (16.8%): 135 patients (83.3%) had ischemic stroke, 14 patients (6.6%) – transient ischemic attack (TIA), 1 patient (0.6%) – stroke and TIA, and 12 patients (7.4%) – peripheral thromboembolic complications.

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**Conclusions.** The majority of hospitalized AF patients evaluated in our study were elderly patients with high risk of thromboembolic complications and chronic arrhythmia. The most common risk factors of thromboembolic complications in the examined group were older age and hypertension. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were higher in patients with AF and impaired renal functions than in patients with AF and normal renal function. Peripheral embolism was identified in every 13<sup>th</sup> patient with thromboembolic complications and AF.

Key words: atrial fibrillation, thromboembolic complications, risk factors

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## Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia, affecting 1.8–2.4% of the adult population. The incidence of AF is constantly growing; the Framingham study demonstrated a significant, almost two-fold increase in the incidence of AF in the population over 75 years of age [1]. The most serious complications of AF are thromboembolic events, especially ischemic stroke. AF is associated with five-fold increase in the likelihood of stroke, and 20% of strokes are caused by AF. Strokes in the course of arrhythmia are associated with higher mortality and disability rates than central nervous system ischemic episodes in patients with sinus rhythm [2, 3]. Most patients with AF have concomitant diseases, mainly hypertension, diabetes and heart failure. The presence of co-morbidities as well as age and gender influence the risk of thromboembolic events [4, 5].

The aim of the study was to determine the prevalence of thromboembolic events and risk factors for their occurrence in patients with AF.

## Material and methods

The study group comprised 962 patients with AF hospitalized in our highly-specialized reference center in 2007–2009. Enrolled in the study were consecutive patients with AF who were hospitalized in order to perform elective or emergency medical procedures. In patients who were hospitalized more than once, only data concerning the last hospitalization were included in the analysis. Exclusion criteria were the valvular etiology of AF (prosthetic valve or severe mitral valve stenosis) and in-hospital death.

To assess thromboembolic risk, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scales were used. In the CHA<sub>2</sub>DS<sub>2</sub>-VASc scale, age over 75 years and prior stroke or transient ischemic attack (TIA, transient ischemic attack) count as 2 points, whereas heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and female sex count as 1 point. 0 scoring in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scales mean low risk of thromboembolic complications, 1 point — moderate risk, 2 points or more — high risk. To assess the risk of bleeding, the HAS-BLED scale was used. Patients with the total score of 0–2 points were considered as having low risk of

bleeding, while those with the score of 3 or more points — as having high risk of bleeding [6]. Glomerular filtration rate (GFR) calculated by MDRD equation was used for the assessment of renal function.

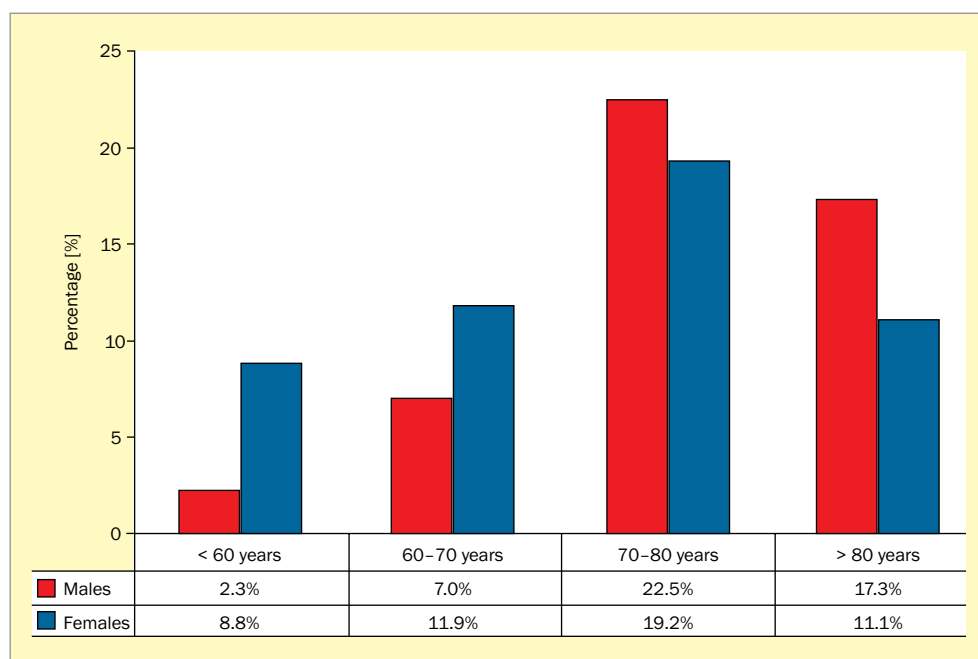
## Results

Among 962 study participants, there were 471 (49%) women and 491 (51%) men. One hundred and seven patients (11.1%) were below 60 years of age, 181 patients (18.8%) were 60–70 years old, 401 patients (41.7%) were between 70 and 80 years, and 273 patients (28.4 %) were above 80 years. Figure 1 shows the distribution of age and sex in the study population.

The most common form of arrhythmia was permanent AF, reported in 467 patients (48.5%). Paroxysmal AF was observed in 423 patients (44%) and persistent AF — in 72 patients (7.5%). Permanent AF occurred in 210 women (44.6%) and in 257 men (52.3%). Paroxysmal AF was diagnosed in 233 women (49.5%) and in 190 men (38.7%). Twenty-six hospitalized women (5.5%) and 46 men (8.8%) had persistent form of AF. In the group with permanent AF, there were 183 patients (39.2%) younger than 75 years and 284 (60.8%) aged ≥ 75 years. In the group with paroxysmal AF, there were 194 patients (45.9%) below 75 years of age and 229 patients (54.1%) aged ≥ 75 years. Persistent form of AF was observed in 52 patients (75.4%) younger than 75 years and 17 patients (24.6%) aged ≥ 75 years. The reasons for hospitalization in the study group are shown in Table 1.

Mean CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in the study population were 2.6 points and 4.2 points, respectively. Thromboembolic risk stratification according to the CHADS<sub>2</sub> scale was as follows: low risk — 93 patients (9.7%), high risk — 869 patients (90.3%), no patient was assigned to the intermediate-risk group. The risk of thromboembolic events in the study group according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc scale was as follows: low risk — 40 patients (4.2%), intermediate risk — 40 patients (4.2%), and high risk — 882 patients (91.7%). Figure 2 shows overall CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in the study group.

The most common disorder, which is also a risk factor for thromboembolic events, was hypertension. Table 2 shows the prevalence of the diseases included in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scales.



**Figure 1.** The distribution of age and gender in the study population

**Table 1.** The causes of hospitalization in the study group

Causes of hospitalization	Number n = 962	Percentage [%]
<b>Urgent</b>		
Cardiac decompensation	280	29.1
Acute coronary syndrome	154	16.0
Atrial fibrillation episode	69	7.2
<b>Elective</b>		
Implantation/reimplantation of a pacemaker/cardioverter- defibrillator	277	28.8
Elective coronary angiography	69	7.2
Electrical cardioversion	44	4.6
<b>Others</b>	69	7.2

The mean value of GFR in the entire study group was 56.85 mL/min. Three hundred and eighty-four patients (39.9%) had GFR above 60 mL/min. The remaining 578 patients (60.1%) had GFR below 60 mL/min. Table 3 compares the number of patients with normal and abnormal renal functions in each thromboembolic risk group.

Overall, thromboembolic complications occurred in 162 patients (16.8%). Acute ischemic stroke was reported in 135 patients, TIA in 14 patients, stroke and TIA in 1 patient, and peripheral thromboembolic complications in 12 patients (including 3 patients who also had ischemic stroke) (Table 4).

In the group of patients with stroke, 76 patients (54.7%) were over 75 years of age and 63 patients (45.3%) were younger than 75 years. TIA occurred in 6 patients (40%) below 75 years of age and in 9 patients (60%) over 75 years of age.

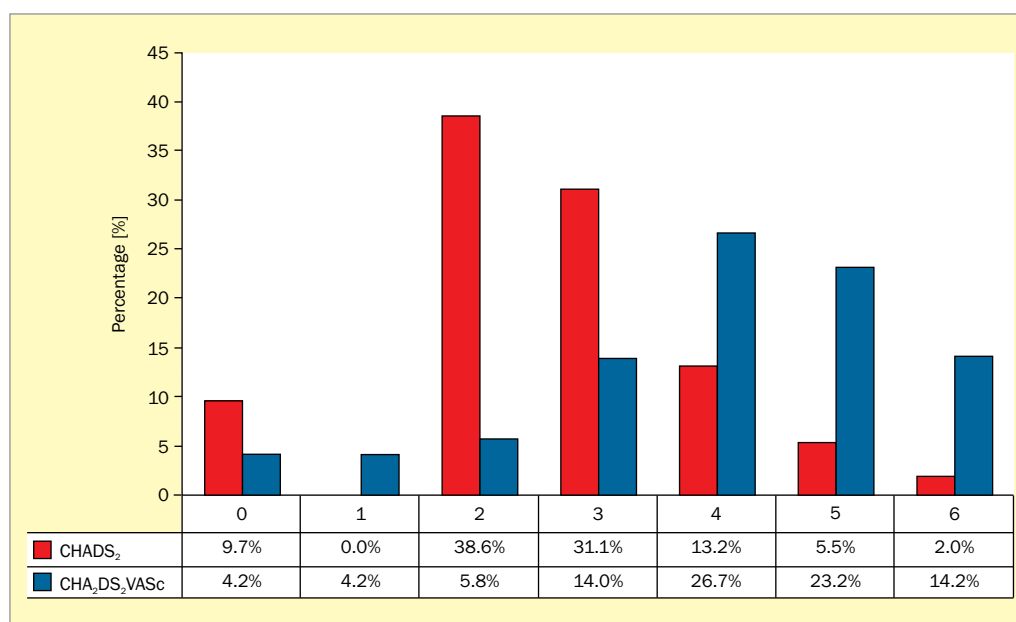
Mean value of GFR in patients with thromboembolic complications was 53.94 mL/min, while in patients without complications it was 57.62 mL/min ( $p = 0.009$ ). GFR below 60 mL/min was found in 119 patients (71.7%) with thromboembolic complications and in 458 patients (57.5%) without thromboembolic complications ( $p = 0.1075$ ).

Comparison of patients with and without thromboembolic complications is presented in Table 5.

## Discussion

AF is the most commonly diagnosed arrhythmia, especially in elderly patients. Unfortunately, the number of patients with AF is constantly increasing [7]. If the incidence of this disease will continue to increase at its current rate, it is expected that AF will be qualified as lifestyle disease like hypertension, diabetes or dyslipidemia [8, 9]. In the ATRIA study it was estimated that in 2050 AF will affect 5.61 million people in the US population [5].

In the present study, which enrolled consecutive hospitalized patients, the proportion of men and women was similar. The Cardiovascular Heart Study also included a similar percentage of women and men with AF [10]. In the Framingham study increase in the incidence of AF in men was observed [4]. Studies involving the population of



**Figure 2.** Distribution of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in the study group

**Table 2.** Co-morbidities included in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scales and age in the study population according to gender

Co-morbidity	Total n = 962	Women n = 471	Men n = 491	P value
Heart failure	618 (64.2%)	300 (63.7%)	318 (64.8%)	0.8715
Hypertension	763 (79.3%)	396 (84.1%)	367 (74.7%)	0.2252
Diabetes	281 (29.2%)	147 (31.2%)	134 (27.3%)	0.3227
Ischemic stroke or TIA	154 (16.0%)	80 (17.0%)	74 (15.1%)	0.4912
Age ≥ 75 years	487 (50.6%)	288 (61.1%)	199 (40.5%)	<b>0.0002</b>
Vascular disease	302 (31.4%)	141 (29.9%)	161 (32.8%)	0.4907
Age				
65–74 years	237 (24.6%)	110 (23.4%)	127 (25.9%)	0.4822

TIA – transient ischemic attack

Western Australia as well as Rochester and ATRIA trials also showed the predominance of men among patients with AF [5, 6, 11]. The Rotterdam study showed that women were more likely to have AF than men [12]. Interestingly, in this study, a higher percentage of women than men were over the age of 75 years. Thus, women in the present study were characterized by a high risk of thromboembolism because of the age and sex.

Age, like the history of thromboembolic episode, is the strongest risk factor for thromboembolic events in patients with AF. In the present study, most patients were elderly. The majority of patients (70%) in the study population were over 70 years of age; slightly more than 1/4 of patients were 80 years and more. A population study on patients with AF also showed that the incidence of AF was increasing

with age [11–13]. In the present study, the mean age of patients with AF was 73 years. In a study of patients with AF hospitalized in 2012–2013 at our center, the average age of the patients was 71.3 years [14]. Therefore, it seems that the profile of hospitalized patients with AF has not changed in recent years. Although it is worth noting that more and more young outpatients are treated for arrhythmia.

Co-morbidities affect the risk of thromboembolic events in patients with AF. In the present study, the most common co-morbidity was hypertension. Similar observations have been reported by Benecka-Majkutewicz et al. [15] who found that hypertension was diagnosed in nearly 80% of the study population. Additionally, it was more common in women. In the ATRIUM registry, hypertension occurred in 82% of patients [16]. Heart failure, another disease affect-

**Table 3.** Comparison of the incidence of impaired renal function in thromboembolic risk groups according to CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores

	Glomerular filtration rate [mL/min]		P value
	≥ 60 n = 384	< 60 n = 578	
Mean CHADS <sub>2</sub>	2.15	2.95	< 0.0001
Mean CHA <sub>2</sub> DS <sub>2</sub> VASc	3.38	4.80	< 0.0001
CHADS <sub>2</sub> = 0			
n = 93	76 (19.8%)	17 (2.9%)	< 0.0001
CHADS <sub>2</sub> = 1	0 (0.0%)	0 (0.0%)	–
CHADS <sub>2</sub> ≥ 2			
n = 869	308 (80.2%)	561 (97.1%)	0.0487
CHA <sub>2</sub> DS <sub>2</sub> VASc = 0			
n = 40	38 (9.9%)	2 (0.3%)	< 0.0001
CHA <sub>2</sub> DS <sub>2</sub> VASc = 1			
n = 40	31 (8.1%)	9 (1.6%)	< 0.0001
CHA <sub>2</sub> DS <sub>2</sub> VASc ≥ 2			
n = 882	315 (82.0%)	567 (98.1%)	0.0632

ting the risk of thromboembolic events, was diagnosed in 2/3 of the patients participating in our study, with similar incidence in women and men. In the ATRIA study, heart failure was observed in 30% of patients [12].

In the studied population, the thromboembolic risk was assessed using CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scales. Almost all patients in the study were at high risk of thromboembolic events both according to the CHADS<sub>2</sub> scale and the CHA<sub>2</sub>DS<sub>2</sub>VASc scale. When assessing the risk in an individual patient, additional risk factors for thromboembolism that may increase the risk significantly, but are not included in the existing scales, should be taken into account. Such a risk factor for thromboembolic events not included in the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VASc scale is chronic kidney disease. A meta-analysis of 284,672 patients performed by Lee et al. [17] showed that patients with eGFR below 60 mL/min/1.73 m<sup>2</sup> were characterized by 43% higher risk of stroke compared with those who had normal baseline eGFR. Piccini et al. [18] proposed including impaired renal function (GFR < 60 mL/min/m<sup>2</sup>) as a thromboembolic risk factor in the CHADS<sub>2</sub> scale. The R<sub>2</sub>CHADS<sub>2</sub> model much better predicted the incidence of stroke than the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VASc scale.

In the study population, impaired renal function occurred in 60% of patients with AF. It may have been caused by the fact that the patients were elderly and therefore their renal function was significantly more commonly impaired. For this study, we use the term 'impaired renal function', not

**Table 4.** Thromboembolic complications in the study population

Complication	Number of patients n = 162	Percentage of patients [%]
Stroke	135	83.3
TIA	14	8.6
Stroke + TIA	1	0.6
Peripheral embolism – total:	12	7.4
• superficial femoral artery	3	1.9
• dorsalis pedis artery	1	0.6
• superficial femoral artery + dorsalis pedis artery	1	0.6
• popliteal artery	1	0.6
• brachial artery	5	3.1
• superior mesenteric artery	1	0.6

TIA – transient ischemic attack

'chronic kidney disease', because the diagnostic criterion for chronic kidney disease is GFR below 60 mL/min/m<sup>2</sup> for at least 3 months. We were not able to compare the GFR within three months in the study population. Interestingly, patients with GFR of less than 60 mL/min had statistically significantly higher mean CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores compared with those with GFR over 60 mL/min. Besides the proved impact of abnormal renal function on the incidence of thromboembolic complications, a GFR can be regarded as an indirect marker, the value of which is negatively correlated with the thromboembolic risk in patients with AF, due to the common pathomechanisms of chronic kidney disease and other conditions affecting the risk of thromboembolic events.

In this study, thromboembolic complications occurred in 17% of patients of hospitalized patients with AF. The majority of patients had ischemic stroke. This finding is similar to the data obtained in the Framingham study [4]. In the ATRIA and Rotterdam trials, lower proportion of patients with ischemic stroke or TIA was reported (about 9%) [5, 11].

In the present study, peripheral embolism was found in 7% of patients with thromboembolic complications. Just as in other studies and registries, peripheral emboli were most often located in the arteries of upper and lower limbs. According to data from Danish registry, the distribution of thromboembolic lesions in the body was as follows: 61% in the upper and lower extremities in, 29% in the mesenteric arteries, 9% in the pelvic arteries, 7% in the aorta, and

**Table 5.** Comparison of patients with and without thromboembolic complications

Clinical features	Patients, total n = 962	With thromboembolic complications n = 166	Without thromboembolic complication n = 796	P value
Women	471 (49.0%)	86 (51.8%)	385 (48.4%)	0.4981
Men	491 (51.0%)	80 (48.2%)	411 (51.6%)	
Age (mean), years	73	77	75	0.3571
<b>Mean score (points)</b>				
CHADS <sub>2</sub>	2.63	4.30	2.29	< 0.0001
CHA <sub>2</sub> DS <sub>2</sub> VASc	4.23	5.89	3.88	< 0.0001
HAS-BLED	2.54	3.14	2.39	< 0.0001
<b>CHADS<sub>2</sub></b>				
0 points	93 (9.7%)	0 (0.0%)	93 (11.7%)	< 0.0001
1 point	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
≥ 2 points	869 (90.3%)	166 (100%)	703 (88.3%)	0.3058
<b>CHA<sub>2</sub>DS<sub>2</sub>VASc</b>				
0 points	40 (4.2%)	0 (0.0%)	40 (5.0%)	0.0040
1 point	40 (4.2%)	0 (0.0%)	40 (5.0%)	0.0040
≥ 2 points	882 (91.6%)	166 (100%)	716 (90.0%)	0.3822
<b>HAS-BLED</b>				
0–2 points	531 (55.2%)	44 (26.5%)	487 (61.2%)	< 0.0001
≥ 3 points	431 (44.8%)	122 (73.5%)	309 (38.8%)	< 0.0001
<b>Atrial fibrillation form</b>				
Paroxysmal	423 (44.0%)	66 (39.8%)	357 (44.8%)	0.4480
Persistent	72 (7.2%)	14 (7.2%)	57 (7.2%)	0.9770
Permanent	467 (48.5%)	87 (52.4%)	380 (47.7%)	0.5234
<b>Co-morbidities</b>				
Heart failure	618 (64.2%)	100 (60.2%)	518 (65.1%)	0.5775
Hypertension	763 (79.3%)	134 (80.7%)	629 (79.0%)	0.8675
Diabetes	281 (29.2%)	54 (32.5%)	227 (28.5%)	0.4485
Age > 75 years	487 (50.6%)	92 (55.4%)	395 (49.6%)	0.4421
Vascular disease	302 (31.4%)	46 (27.7%)	256 (32.2%)	0.4115
Age 64–75 years	237 (24.6%)	42 (25.3%)	195 (24.5%)	0.8653

2% in the renal artery [19]. Peripheral embolism can be oligosymptomatic, hence it may be undiagnosed. Renal or mesenteric artery embolism often remains undiagnosed. It is possible that in the present study the real percentage of patients with peripheral arterial embolism was also higher than reported.

In a study comparing patients with and without thromboembolic complications, 74% of patients who had stroke, TIA, or peripheral embolism, were also at high risk of bleeding complications. Factors included in the HAS-BLED scale (hypertension, impaired kidney and liver functions, stroke, history of bleeding episodes, unstable INR values,

age over 75 years, alcohol and drugs — acetylsalicylic acid, non-steroidal anti-inflammatory drugs) are also risk factors for thromboembolic events.

Our paper presents a population of hospitalized AF patients with particular reference to thromboembolic risk assessment and thromboembolic complications reported. It is worth to remember that when assessing the risk of stroke in AF patients, careful evaluation should include not only the conventional risk factors, but also co-morbidities that are not included in the generally applicable scales but significantly affect the risk of thromboembolic events, i.e. chronic kidney disease or malignancy.



## Conclusions

1. The majority of hospitalized patients with AF were over 70 years of age, at high risk of thromboembolic complications and with the permanent form of arrhythmia. 2. The most common risk factor for thromboembolic complications in the study group was older age and hypertension. There was a predominance of women in the group of elderly patients. 3. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores were higher in patients with AF and impaired renal function than in patients with AF

and normal renal function. 4. Peripheral embolism occurring in every 13<sup>th</sup> patient with thromboembolic complications usually involved upper and lower limb arteries. The clinical manifestation of systemic embolism may be unusual or even oligosymptomatic, and therefore the proportion of patients with peripheral embolism may be underestimated.

## Conflict of interest(s)

The authors declared no conflicts of interest(s).

## Streszczenie

**Wstęp.** Powikłania zakrzepowo-zatorowe są najpoważniejszymi powikłaniami migotania przedsionków (AF). Najczęściej dotyczą one ośrodkowego układu nerwowego, choć zatory mogą być także zlokalizowane w tętnicach obwodowych. Celem badania było określenie częstości występowania powikłań zakrzepowo-zatorowych oraz identyfikacja czynników ryzyka ich wystąpienia u hospitalizowanych chorych z AF.

**Materiały i metody.** Badaną grupę stanowiło 962 chorych z niezastawkowym AF hospitalizowanych w referencyjnym ośrodku kardiologicznym w latach 2007–2009. Ryzyko zakrzepowo-zatorowe u chorych z AF określono za pomocą skal CHADS<sub>2</sub> i CHA<sub>2</sub>DS<sub>2</sub>VASc.

**Wyniki.** W badanej grupie 962 chorych z AF najwięcej, bo 674 chorych (70%), miało powyżej 70 lat i występowała u nich utrwalona postać arytmii – 467 osób (48,5%). Nie stwierdzono różnic w zakresie częstości występowania arytmii u kobiet i mężczyzn. Większość badanych była obciążona wysokim ryzykiem zakrzepowo-zatorowym; w skali CHADS<sub>2</sub> – 869 chorych (90,3%), w skali CHA<sub>2</sub>DS<sub>2</sub>VASc – 882 chorych (91,7%). Średni wynik w skali CHADS<sub>2</sub> wynosił 2,4 pkt., natomiast w skali CHA<sub>2</sub>DS<sub>2</sub>VASc 4,2 pkt. Najczęściej występującym schorzeniem, a jednocześnie czynnikiem ryzyka zakrzepowo-zatorowego zgodnie ze skalą CHADS<sub>2</sub>, było nadciśnienie tętnicze – 763 chorych (79,3%). U większości chorych, tj. u 578 (60,1%), stwierdzono jednocześnie nieprawidłową funkcję nerek. Powikłania zakrzepowo-zatorowe wystąpiły u 162 chorych (16,8%): u 135 chorych (83,3%) – udar niedokrwienny mózgu, u 14 chorych (6,6%) – przemijający napad niedokrwienny (TIA), u 1 chorego (0,6%) – udar mózgu i TIA, a u 12 chorych (7,4%) – obwodowe powikłania zakrzepowo-zatorowe.

**Wnioski.** W grupie hospitalizowanych chorych z AF większość badanych stanowili pacjenci w podeszłym wieku, obciążeni wysokim ryzykiem powikłań zakrzepowo-zatorowych i z utrwaloną postacią arytmii. Najczęściej występującym czynnikiem ryzyka wspomnianych powikłań w badanej grupie były podeszły wiek oraz nadciśnienie tętnicze. Wyniki w skalach CHADS<sub>2</sub> oraz CHA<sub>2</sub>DS<sub>2</sub>VASc były wyższe u chorych z AF i upośledzoną funkcją nerek niż u chorych z AF i prawidłową funkcją nerek. Zatorowość obwodowa występowała u co 13. chorego z powikłaniami zakrzepowo-zatorowymi i AF.

Słowa kluczowe: migotanie przedsionków, powikłania zakrzepowo-zatorowe, czynniki ryzyka

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